INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Pharmacovigilance and Over Counter Drugs Ensuring Safety

Vrushali Gaikwad*, Sonal Kumbhar, Dr. Nilesh Chougule

Ashokrao Mane Institute of Pharmacy, Ambap, Kolhapur, Maharashtra, India. 416112.

ARTICLE INFO

Published: 10 Dec. 2024
Keywords:
Pharmacovigilance, over-the-counter drugs, paracetamol, ibuprofen, safety monitoring, adverse drug reactions, public education, post-market surveillance
DOI:
10.5281/zenodo.14361696

ABSTRACT

Pharmacovigilance is critical for monitoring the safety and efficacy of all pharmaceutical products, including over-the-counter (OTC) drugs like paracetamol (acetaminophen) and ibuprofen, which are commonly used for pain relief and fever reduction. Although these medications are available without a prescription, their widespread use presents potential risks due to improper dosing, drug interactions, and the lack of professional oversight. This review examines the role of pharmacovigilance in ensuring the safety of OTC drugs, specifically focusing on paracetamol and ibuprofen, two of the most frequently used analgesics globally. Paracetamol, widely regarded as a safe option when used appropriately, can cause severe liver toxicity in cases of overdose, often due to consumer misjudgment or lack of awareness regarding safe dosage limits. Conversely, ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), poses risks related to gastrointestinal bleeding, renal impairment, and cardiovascular events, especially when used long-term or in higher-than-recommended doses. Pharmacovigilance systems, such as spontaneous reporting of adverse drug reactions (ADRs) and post-market surveillance, are essential for detecting and addressing safety concerns associated with these OTC drugs. This review also highlights the challenges faced by regulatory bodies and healthcare providers in tracking ADRs for OTC drugs. The relatively low rate of reporting ADRs by consumers, coupled with limited healthcare interventions for OTC drug users, complicates the ability to detect potential safety signals. Additionally, the risk of polypharmacy and drug interactions is higher in self-medication practices, further emphasizing the need for increased pharmacovigilance. To improve safety outcomes, the review suggests several strategies, including the enhancement of public education regarding safe use, the development of digital tools for ADR reporting, and the expansion of integrated surveillance systems that track the safety profiles of commonly used OTC medications. By strengthening pharmacovigilance efforts and fostering a more informed public, the risks associated with paracetamol, ibuprofen, and other OTC drugs can be minimized, ensuring safer use and better health outcomes for consumers.

***Corresponding Author:** Vrushali Gaikwad
Address: Ashokrao Mane Institute of Pharmacy, Ambap, Kolhapur, Maharashtra, India. 416112
Email ✉: vrushaligaikwad448@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Pharmacovigilance, according to the World Health Organization (WHO), is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" [1]. Pharmacovigilance support the safe and appropriate use of medications by: a) promoting the detection of previously unidentified ADRs and interactions as well as increases in the frequency of known ADRs; b) identifying risk factors for the development of ADRs; and c) estimating quantitative aspects of benefit/risk analysis and disseminating information to improve drug prescribing and regulation. [2] "Over the counter (OTC) Drugs" refers to medications that are legally permitted to be sold "over the counter," that is, without a registered physician's prescription. All medications that are not on the list of "prescription drugs" are regarded as non-prescription drugs (also known as over-the-counter, or OTC) in India, even though the term does not have legal recognition. Prescription medications are classified under Schedules H and X of the Drug and Cosmetics Rules of 1945. [3] Generally speaking, over-the-counter medications must be demonstrated to be reasonably safe and well accepted, and they must be used largely to treat conditions that do not require direct medical care.[4] OTC drugs, which are accessible to consumers without a prescription, are thought to be reasonably safe and appropriate for use without a doctor's oversight [5]. The WHO Anatomical Therapeutic Chemical (ATC) classification divides medications into ten groups: analgesics, laxatives, antithrombotic agents, antacids, cough and cold preparations, antihistamines, dermatologicals, throat preparations, nose preparations, and antidiarrheals. [6] Acetaminophen, often known as paracetamol or N-acetyl-p-aminophenol, is one of the most popular over-the-counter analgesics and antipyretics. It was initially produced in 1893 by Joseph von Mering by the reaction of p-nitrophenol with tin and glacial acetic acid. For many years to come, paracetamol is expected to remain the preferred drug for treating fever and excruciating pain [7]. Analgesics are among the most often used drugs worldwide [8]. Acetaminophen, also referred to as paracetamol, is a moderate analgesic that is commonly used because of its effectiveness, low incidence of side effects, and excellent patient tolerance [9]. Inflammation, fever, and pain are treated with ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID).[10] This includes migraines, painful menstruation, and rheumatoid arthritis.[10] The patent ductus arteriosus of a premature infant can also be sealed with it [11]. [10] Both oral and intravenous administration are possible.[10] In 1969 and 1974, respectively, ibuprofen was first made available in the UK and the USA to treat rheumatoid arthritis. In the end, it received a patent in 1961. In terms of over-the-counter sales, it was the first NSAID.[12]

Over The Counter Drugs

Over-the-counter (OTC) drugs are those that are sold directly to patients without a prescription from a qualified medical practitioner. For minor illnesses like a cold or cough, headache, backache, toothache, muscle aches, menstrual cramps, fever, etc., we frequently see a pharmacist rather than a doctor. [89] These over-the-counter (OTC) drugs are widely available to the general public without a doctor's prescription and are believed to be both safe and effective. These are mostly used for relief of symptoms; they are not meant to take the place of prescription drugs. [90] These over-the-counter medications save time in hospitals, reduce the need for expensive consultations, and eliminate long lines at doctor's offices.[91] Many teenagers and young adults buy and take over-the-counter medications, and some of them could take them without first reading the instructions.[92]

Reasons For Self-Medication

India, a nation with a large population, struggles with an extremely low doctor-to-patient ratio, which fosters a culture that encourages the use of over-the-counter medications. The following is a list of several specific explanations for the same:
1. Possessing an old prescription
2. Conserving time
3. Advice from family members
4. Expensive doctor visits 5. Congested hospitals
6. A pharmacist's advice
7. Ignorance, poverty, and false beliefs
8. A lot of advertising
9. Additional causes.[93]

The guidelines for choosing on using OTC drugs are as follows

• To prevent more health issues, self-diagnosing should be as exact as possible and not predicated on conjecture.
• Choose goods that don't contain any allergens and have a small number of suitable ingredients. Increased risk and treatment expenses result from the use of needless medications caused by more active components.
• Carefully read the label to ascertain the appropriate dosages, adverse effects, and contraindications.
• If you are unsure about the medication, ask a doctor or pharmacist.
• In the event of polypharmacy, look for potential drug interactions with other medications.
• Follow the dosage exactly, and if the symptoms don't go away, see a doctor or pharmacist.
• Don't take over-the-counter medications for longer than is advised. If the problem does not improve, see a doctor or pharmacist right away.[94]

Effect Of Over Counter-Drugs on Health

Because improper pharmaceutical use exposes the consumer to harm without their understanding, it is clinically undesirable. Benefits are not guaranteed, and it may be detrimental in several ways. Concerns about OTC side effects resulting from pharmaceutical resistance and reliance, especially on sedatives, laxatives, analgesics, and antacids, are growing quickly.[95] In small dosages, over-the-counter epinephrine is thought to be safe and effective, but when misused or mistreated, it can cause serious injury. One of the most likely effects can be death.[96]

According to previous coroner's inquests, OTC painkillers such as Due to OTC addiction, Ibuprofen and codeine are responsible for the deaths of 49-year-old and 41-year-old users who passed away from respiratory depression and renal failure, respectively. Co-proxamol, an analgesic combination that comprises paracetamol and the opioid dextropropoxyphene, is one of the few over-the-counter drugs that are removed from the market for safety reasons.[90] Paracetamol is currently advertised as an analgesic and antipyretic, to be used for no more than 3 days without contacting a doctor.[97] A prescription medication called paracetamol is used to treat fever and temporary pain. It falls under the acetaminophen category. [98] It is effective in:

- treating fever and
- mild to moderate discomfort.
- severe pain (when taken with codeine);
- headache
- Flu and colds (when taken with decongestants and antihistamines).[99]

Table1: Commonly seen OTCs

Symptoms	Medications
Cough/Cold/Fever	Chlorpheniramine maleate, Phenylephrine, Pheniramine, paracetamol

Headaches/Body aches/sprains	Ibuprofen, Ibuprofen + paracetamol , Diclofenac
GI ailments like hyperacidity/ Constipation/diarrhea /nausea	Psyllium, Methyl cellulose, polycarbophil
Pain relivers	Acetaminophen, ibuprofen
Nasal decongestants	Pseudoephedrine
Motion sickness pills	Dimenhydrinate and Diphenhydramine

Paracetamol

Acetaminophen, sometimes referred to as paracetamol, is a non-opioid analgesic and antipyretic medication used to treat fever and mild to moderate pain. [13] [14] [15] This over-the-counter drug is frequently used. Panadol and Tylenol are common brand names. There are three kinds of paracetamol; oral, suppository, and intravenous. [16] In the US, intravenous paracetamol is marketed under the Ofirmev brand.[17]

Why is paracetamol available over the counter?

Acetaminophen, another name for paracetamol, is categorized as an over-the-counter (OTC) medication since it is available without a prescription from a medical professional. This classification is based on several important factors:

Safety Profile: For common conditions like fever, mild to moderate discomfort, and headaches, paracetamol is generally thought to be safe when taken as directed. It has been in use for many years and has a proven safety record in healthy people.

Low Risk of Abuse: One of the criteria used to determine an over-the-counter (OTC) status is the likelihood of abuse or dependence, which paracetamol does not have in contrast to some painkillers or drugs that may be prone to abuse or addiction (such as opioids).

It can be used to treat a wide range of mild symptoms, including fever reduction and headache, muscular, and toothaches. It frequently serves as the initial treatment for these symptoms.

Easy Usage: Paracetamol is excellent for over-the-counter (OTC) sales since it comes in a variety of formulations (tablets, liquid, and suppositories) and is simple for consumers to self-administer.

Minimal Risk of Adverse Effects (When Used Properly): Paracetamol has virtually no adverse effects when taken in the recommended dosages. However, since large dosages can harm the liver, it's crucial to avoid doing so. Because of this risk, there may be restrictions on dosages or pack sizes, as well as explicit dosing instructions.

Chemical and physical properties of paracetamol

A] Description: Big monoclinic prisms from water; white, odourless crystalline powder

B] 169–170.5°C is the melting point.

C] PH at 25°C: 5.3 to 6.5.

D] Density: 1.293 grams/cc

E] Solubility: Soluble in water (1:70, 1:20 at 100°C), ethanol (1:7), acetone (1:13), chloroform (1:50), glycerol (1:40), methanol (1:10), propylene glycol (1:9) and solutions of alkali hydroxides; insoluble in diethylether. In ether, slightly soluble. It is insoluble petroleum ethers, pentone and benzene.

F] Stability: Dry, pure paracetamol is stable to 45°C

G] Dissociation constant: pKa = 9.0-9.5

H] Partition coefficient: Pc = 6.237 (octanol: pH 7.2 buffer)

Mechanism of Action

Uncertainty surrounds the processes underlying paracetamol's analgesic action, which may include both the peripheral and central nervous systems [18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,3

3]. Aspirin (acetylsalicylic acid) also inhibits the formation of prostaglandins and pro-inflammatory mediators, which are widely believed to be reduced in tissue amounts by paracetamol. However, paracetamol does not block the creation of pro-clotting thromboxanes and does not have a substantial anti-inflammatory effect like aspirin does. Paracetamol may work through two main different molecular mechanisms, notwithstanding its ability to inhibit cyclooxygenase (COX) enzymes [18,19,20,21,22,23]. NSAIDs selectively inhibit the conversion of arachidonic acid to prostaglandin G/H, an unstable molecule that is quickly converted into other pro-inflammatory derivatives, which is facilitated by the COXs (prostaglandin G/H synthase enzymes), of which there are two types: COX-1 and COX-2. The antipyretic, analgesic, and anti-inflammatory effects of NSAIDs are believed to be mediated by inhibition of COX-2. Aspirin acetylates the isozymes in the aspirin-binding channel, making it an irreversible, non-competitive inhibitor via decreasing the peroxide site of the enzymes, paracetamol functions as a non-competitive reversible inhibitor [19,22]. The complex "central," spinal, and supraspinal activities of paracetamol are believed to be mediated via cholinergic, noradrenergic, opioid, and serotoninergic (5-HT) pathways [21].

Pharmacokinetic

When taken orally, the stomach often absorbs paracetamol, whereas the small intestine absorbs it quickly. As a result, stomach emptying affects absorption rate. Although food slows down the stomach's absorption and emptying, the overall amount absorbed remains constant. [34] When fasting, the maximal plasma concentration of paracetamol was reached after 20 minutes, however when fed, it was reached after 90 minutes. Foods high in carbohydrates (but not high in protein or fat) reduce the peak plasma concentration of paracetamol by a factor of four. The rate at which paracetamol is absorbed varies depending on the formulation, even when fasting. It takes 20 to 1.5 hours to achieve the maximal plasma concentration. [35] The dose-dependent bioavailability of paracetamol rises from 63% at 500 mg to 89% at 1000 mg. [35] Its distribution volume is approximately 50 L, and its plasma terminal elimination half-life is between 1.9 and 2.5 hours [35].[36] Except in cases of overdose, where it may reach 15–21%, protein binding is minimal. [35] Following a normal dosage of paracetamol, the concentration in serum typically peaks below 30 μg/mL (200 μmol/L). [37] The concentration is often less than 10 μg/mL (66 μmol/L) after 4 hours. [37] Glucuronidation and sulfation are the main liver metabolisms of paracetamol, and the byproducts are subsequently excreted in the urine.

Interaction

Metoclopramide shortens the time (tmax) to the highest blood plasma concentration (Cmax) of paracetamol, increases Cmax, and speeds up stomach emptying. Drugs that impede stomach emptying, like morphine and propantheline, increase tmax and decrease Cmax. [38][39] The clinical significance of interactions with metoclopramide and propantheline is unknown, however interactions with morphine may cause patients to not reach the therapeutic concentration of paracetamol.[39] Ranitidine caused a 1.6-fold rise in the area under the curve (AUC) of paracetamol. Cisapride and nizatidine also cause elevations in AUC. These medications' inhibition of paracetamol's glucuronidation explains the impact. [39] By preventing its sulfation, paracetamol increases ethinylestradiol plasma concentrations by 22%. [39]

Adverse Effect

The frequency of gastrointestinal side effects, such as nausea and abdominal pain, is incredibly low compared to ibuprofen. [40] There may be a rise in risk-taking behavior. [41]

The majority of data about the long-term safety of paracetamol comes from observational studies because controlled studies are not available. [40] These show a continuous pattern of increased mortality along with adverse effects on the kidneys, gastrointestinal tract (bleeding, ulcers), and cardiovascular system (stroke, myocardial infarction) with higher doses of paracetamol.[42][40][43] A 1.9-fold increased incidence of peptic ulcer is linked to paracetamol use. [40] The risk of gastrointestinal bleeding and other bleeding events is increased by 3.6–3.7 times for those who take it frequently at a higher dose (more than 2-3 g daily).[44] Blood pressure and heart rate are slightly but noticeably raised by paracetamol.[40] The safety of paracetamol during pregnancy has come under closer examination. The use of paracetamol during the first trimester does not seem to be associated with unfavorable pregnancy outcomes or birth abnormalities. Nonetheless, there are signs that long-term paracetamol usage during pregnancy may raise the risk of asthma and developmental and reproductive problems in the children of those mothers.[44] Pregnancy-related paracetamol consumption by the mother is linked to an elevated risk of asthma in children, [45][46] However, it is challenging to distinguish between these factors, as are the maternal diseases for which paracetamol may be treated. [44] Stevens Johnson Syndrome (SJS) is an uncommon hypersensitivity reaction and severe skin and mucous membrane condition that can be fatal. The American doctors Frank Chambliss Johnson and Albert Mason Stevens, who both reported on SJS in the American Journal of Diseases of Children in 1922, are honored by the name of the disorder. [47] The condition can be classified as SJS (30% BSA) based on the involvement of body surface area (BSA). This indicates that as the percentage of skin involvement increases, the severity and prognosis of the disease worsen.[48] Although SJS is often an immune system condition, medication consumption is linked to over 80% of SJS occurrences. [49] Only a small number of SJS case reports are linked to paracetamol use. We gave a brief account of an unusual incidence of SJS brought on by taking paracetamol tablets.

Medical Uses

Fever

The purpose of paracetamol is to lower fever.[13] Its antipyretic qualities, especially in adults, have not been thoroughly studied, hence its advantages are unknown.[50] It has been said to be overprescribed for this use as a result. [50] Furthermore, poor quality clinical data suggests that paracetamol may alleviate a runny or stuffy nose when used to treat the common cold, but not other cold symptoms including coughing, sneezing, malaise, or sore throat.[51]

Pain

Mild to moderate pain, including headaches, muscle pains, toothaches, mild arthritis, and discomfort from colds, the flu, sprains, and dysmenorrhea, can be relieved with paracetamol. [52] It is especially advised for mild to moderate acute pain because there is not enough evidence to support its use in treating chronic pain.[53]

Headache

Acute migraines can be effectively treated with paracetamol: 39% of patients report pain alleviation after an hour, compared to 20% in the control group [54]. [55] As a first-line treatment for migraines, the combination of aspirin, paracetamol, and caffeine "has strong evidence of effectiveness."[56]

The science and practices involved in identifying, evaluating, comprehending, and preventing side effects or other drug-related issues are known as pharmacovigilance. Pharmacovigilance is particularly crucial when it comes to paracetamol (acetaminophen) because of its widespread usage and the

possibility of hepatotoxicity (liver damage) at high dosages.

Here's the detailed procedure for pharmacovigilance of paracetamol:

1.Pre-Marketing Phase (Clinical Trials)

Clinical trials are used to assess the safety of any medication, including paracetamol, before it is put on the market. Preclinical Studies: Using animals to test for toxicity and safety. Clinical Trials in Phase I: To assess the pharmacokinetics (absorption, distribution, metabolism, and excretion) and safety of paracetamol, a small group of healthy volunteers will be used. Phase II Clinical Trials: Presented to a broader patient population in order to assess effectiveness and further track safety, including the detection of typical adverse effects. Phase III clinical trials are carried out on a broader population with a range of demographics in order to verify safety and efficacy and find less frequent adverse effects.

2. Post-Marketing Surveillance (PMS)

Pharmacovigilance is necessary to track paracetamol's long-term safety in the general population after it is authorized and put on the market. The actions consist of:

A. Spontaneous Reporting System (SRS)

Patients and medical professionals should report any paracetamol adverse drug reactions (ADRs). Regulatory agencies like the FDA (USA), MHRA (UK), CDSCO (India), or EMA (EU) gather these reports. Channels for Reporting: Online forms, smartphone apps, or specialized websites like the WHO's VigiBase can be used for this. ADR Types Reported: Common side effects like rash and nausea as well as more significant ones like hepatotoxicity and Stevens-Johnson syndrome might be reported.

B. Data Collection & Signal Detection

Signal Detection: Any novel safety signals—unexpected or elevated risks not identified in clinical trials—are continuously monitored by the pharmacovigilance system. Signal Evaluation: Additional research is started if a pattern or signal appears, such as an unusual rise in complaints of liver failure linked to paracetamol use.

C. Risk Management Plan (RMP)

The purpose of a paracetamol risk management plan is to reduce possible hazards, especially those connected to liver damage from overdose. Labeling Updates: It might be suggested that product labels or patient pamphlets be updated to include cautions regarding taking more medication than is advised.

D. Periodic Safety Update Reports (PSUR)

PSURs must be submitted to regulatory bodies by pharmaceutical companies. ADRs, safety issues, and modifications to product labeling are among the global post-market monitoring data that are compiled in these reports.

3. Pharmacoepidemiological Studies

Pharmacoepidemiological studies are carried out to determine the severity of the issue if a new danger appears: Case-control studies or cohort studies: These studies aid in identifying the relationship between the usage of paracetamol and particular adverse drug reactions, such liver damage.

4. Regulatory Action

Based on the findings, regulatory authorities may: Issue Safety Alerts: Inform healthcare providers and the public of new risks associated with paracetamol. Labeling Updates: Update safety warnings, contraindications, or dosage instructions on paracetamol products. Market Withdrawal: In rare cases of serious risk, a product may be temporarily or permanently removed from the market.

5. Post-Market Risk Minimization

To reduce adverse outcomes, measures such as: Educational Campaigns: Healthcare providers are educated about risks of paracetamol, especially for patients with liver conditions or those using multiple products containing acetaminophen.

Packaging Adjustments: Limiting the number of tablets in a package or making blister packs more prevalent to reduce the likelihood of overdose.

6. Global Coordination (WHO, Uppsala Monitoring Centre)

Paracetamol safety data is shared globally through systems like the WHO's Uppsala Monitoring Centre (UMC). This allows for the pooling of data and identification of risks at an international level.

Future Perspectives with paracetamol

Acetaminophen, sometimes known as paracetamol, is a well-known over-the-counter antipyretic analgesic medication. New formulations that achieve prolonged absorption to prolong the duration of action for regular long-term administration and rapid absorption for a quick beginning of action are probably in the works. Rectal administration also calls for improved dose formulations. The use of intravenous paracetamol as a postoperative analgesic and for fever control in the intensive care unit has significantly increased since its availability. Although intravenous paracetamol is currently only available in a small number of countries, its future widespread marketing seems certain. The misuse of paracetamol as a fashionable agent for self-poisoning seems likely to continue, and liver failure may still occur in the small proportion of overdose patients who present too late for effective antidotal treatment with N-acetylcysteine. Much effort is being devoted to the study of the molecular mechanisms of paracetamol hepatotoxicity, and it is hoped that further advances may make it possible to prevent liver failure in all patients, irrespective of delays in presentation. At the same time, there is great interest in the mechanisms of the therapeutic actions of paracetamol and its effects on the different isoforms of cyclo-oxygenase. There will probably be important new findings in this area and these may lead to wider clinical use. Meantime, possible novel therapeutic applications for paracetamol include its use as an antioxidant to prevent atherosclerosis and cardiovascular disease by inhibiting the oxidation of low-density lipoproteins, and to prevent the formation of cataracts.

Ibuprofen

In 1961, while working at Boots UK Limited, Stewart Adams and John Nicholson [58] discovered ibuprofen, which was first sold under the brand name Brufen.[58] The most often prescribed and used NSAID is ibuprofen. It is a very popular over-the-counter drug that is used as an antipyretic, an analgesic, and an anti-inflammatory. [59] Ibuprofen is an anti-inflammatory and pain reliever. It functions by inhibiting the cyclo-oxygenase enzyme, which generates prostaglandins, which are chemicals implicated in pain and inflammation. Ibuprofen is an ingredient in medications that treat fever, inflammation, and discomfort.

Why is ibuprofen available over the counter?

Ibuprofen is regarded as an over-the-counter (OTC) medication since it is available without a prescription from a medical professional. Based on the fact that ibuprofen is generally safe for most individuals to use for the treatment of common diseases like pain, fever, or inflammation when taken as directed and in accordance with the recommended dosage, this classification was made.

Here are a few key reasons why ibuprofen is available OTC:

1. Safety Profile: Ibuprofen has a well-established safety profile for short-term use when taken as prescribed. While moderate side effects like nausea or sensations of lightheaded are common, prolonged or excessive use usually carries substantial hazards.

2. Low Risk of Abuse: Ibuprofen has a low risk of addiction or misuse, making it appropriate for most people to take unsupervised, when compared to certain more potent painkillers like narcotics.

3. Effectiveness for Common Conditions: It is a practical choice for self-care because it works well for common ailments like fever, headaches, menstrual cramps, mild arthritis, and muscular soreness.

Even though ibuprofen is an over-the-counter medication, it's crucial to use it sensibly because prolonged or excessive use might result in negative side effects like kidney or gastrointestinal problems or an increased risk of heart-related disorders. Always abide by dose instructions, and if you have any questions or concerns about any previous problems, speak with your doctor.

Chemical and physical properties of Ibuprofen

Formula: $C_{13}H_{18}O_2$

Molar Mass: 206.285 $g \cdot mol^{-1}$

Density: 1.03 g/cm^3

Melting point: 75 to 78 °C (167 to 172 °F)

Boiling point: 157 °C (315 °F) at 4 mmHg

Solubility in water: 0.021 mg/mL (20 °C)

Mechanism Of Action

Inhibiting the cyclooxygenase (COX) enzymes, which change arachidonic acid into prostaglandin (PGH2), is how NSAIDs like ibuprofen function. Other enzymes then transform PGH2 into thromboxane A2, which promotes platelet aggregation and causes blood clots, and a number of other prostaglandins, which act as mediators of pain, inflammation, and fever. NSAIDs appear to primarily work by inhibiting COX-2, which lowers the production of prostaglandins that mediate inflammation, pain, fever, and swelling. This mechanism underlies the analgesic, antipyretic, and anti-inflammatory effects of NSAIDs. The hypothalamus may be the site of antipyretic actions, which include vasodilation, increased peripheral blood flow, and consequent heat dissipation. Instead, undesirable effects on the gastrointestinal tract would be caused by inhibition of COX-1.[60]. However, it is unclear how each COX isoform contributes to the analgesic, anti-inflammatory, and gastric damage actions of NSAIDs, and various substances result in varying degrees of gastric damage and analgesia. [61]

Pharmacokinetic

Absorption: When used orally, ibuprofen is quickly and fully absorbed. However, because food intake alters the pH, emptying, and motility of the stomach, it can impact absorption. Ibuprofen's maximum plasma concentration (Cmax) is lowered by 30% to 50% and its duration to maximum concentration (Tmax) is postponed by 30 to 60 minutes when taken with food.

Distribution: Approximately 99% of ibuprofen is linked to plasma proteins after absorption.

Metabolism: The two main types of metabolites that are produced when ibuprofen is metabolized are hydroxylated and carboxylated molecules. The main CYP enzymes in charge of ibuprofen clearance are CYP2C9 and CYP2C8. [62, 63]

Elimination: The main way that ibuprofen is eliminated from the body is through urine as conjugates and metabolites. Roughly 1% of the initial medication is eliminated unaltered.[64]

Drug Interaction:

ACE inhibitors: Ibuprofen may lessen ACE inhibitors' antihypertensive effects. For patients taking these drugs at the same time, monitoring is advised.

Aspirin: Ibuprofen may counteract the antiplatelet effects of aspirin, particularly if taken concurrently with or prior to aspirin. Immediate-release low-dose aspirin should be administered at least two hours before to ibuprofen in order to reduce this interaction. Because of the elevated cardiovascular risks, concurrent usage is generally not advised.

Diuretics: Ibuprofen may lessen the effectiveness of diuretics like furosemide and thiazides by decreasing their natriuretic action. Patients taking these drugs at the same time need to be closely watched because they are more likely to develop AKI.[65]

Lithium: Ibuprofen inhibits renal prostaglandin formation, which raises plasma lithium levels and lowers renal lithium clearance. Patients should be closely watched for symptoms of lithium toxicity when using ibuprofen and lithium combined.[66]

Anticoagulants: In patients on warfarin medication, ibuprofen raises the risk of gastrointestinal bleeding.[67] When these drugs are taken combined, patients should be cautiously watched for bleeding symptoms.

Adverse Effect

High blood pressure, headache, dizziness, rash, gastrointestinal ulcers, nausea, heartburn, indigestion, diarrhea, constipation, and salt and fluid retention are among the side effects. [68][69][70]

Esophageal ulcers, heart failure, elevated potassium levels, renal impairment, disorientation, and bronchospasm are uncommon side effects. [69] Ibuprofen can occasionally make asthma worse.[71] Breathing problems, shock, blistering, skin reddening, rashes, hives, and asthma (wheezing) are some of the symptoms of an ibuprofen allergy. [72] Ibuprofen over-the-counter use without a prescription raises the possibility of excessive dosages and infrequent doses, which can lead to gastrointestinal issues.[73] Ibuprofen's strong protein binding results in hyperbilirubinemia and bilirubin displacement when administered intravenously to treat patent ductus arteriosus (PDA).[74]

The course of a pediatric patient who presented with DRESS syndrome in 2016 was reported in a case report, however there is little information available about ibuprofen-induced DRESS syndrome. A patient who consumed an over-the-counter medication containing ibuprofen for 20 days got a drug-induced liver damage with multiform exudative erythema, according to another report from 2014.[75]

Patients who have eye issues should discontinue taking ibuprofen. As with all NSAIDs, kidney-related side effects include nephritic syndrome, interstitial nephritis, and acute renal failure, however these are quite uncommon. [76]

Medical uses:

Fever (including post-vaccination fever), mild to moderate pain (including post-operative pain), uncomfortable menstruation, osteoarthritis, dental pain, headaches, and kidney stone pain are the main conditions for which ibuprofen is prescribed. persons who don't react favorably to one NSAID may react to another; approximately 60% of persons react to any NSAID. [77] Rheumatoid arthritis and juvenile idiopathic arthritis are two inflammatory conditions for which it is utilized.[78][69] Additionally, it is used to treat patent ductus arteriosus and pericarditis. [11][79] [80]

Dental pain:

One of the most popular and efficient NSAIDs for treating dental pain is ibuprofen.[81] Following third molar surgery, an effective analgesic for managing postoperative pain is 400 mg of ibuprofen.[82] Ibuprofen 400 mg in a liquid gel form relieves post-operative dental pain more quickly and effectively overall.[83]

Patent Ductus arteriosus (PDA)

In premature newborns, this is a common problem. The current standard of medical treatment is intravenous indomethacin.[84] Other PG inhibitors, including ibuprofen, have been investigated for the closure of the ductus arteriosus due to the negative effects of indomethacin; the findings showed that ibuprofen is just as effective as indomethacin.[85]

Cystic fibrosis (CF)

It has also been demonstrated that high doses of ibuprofen can effectively reduce inflammation, most likely via reducing the infiltration of polymorphonuclear cells into the lungs.[86] Patients with cystic fibrosis have a minimal chance of experiencing gastrointestinal adverse effects from large doses of ibuprofen medication. [87][88]

Fever

NSAIDs are frequently used to treat fever in children, and current studies are aimed at improving ibuprofen's ability to treat pediatric fever. There was insufficient evidence in a 2017 literature review to support the idea that ibuprofen and acetaminophen (paracetamol) are more effective at treating fever. Although six of the trials included in this evaluation indicated a slight advantage for ibuprofen, this was not enough to establish that ibuprofen was the better course of action.[100] In a separate trial, alternating dosages of acetaminophen and ibuprofen caused better results for refractory fevers than monotherapy. Only individuals who had a favorable response to the initial treatment cycle, nevertheless, showed this.[111].

Ibuprofen, a popular nonsteroidal anti-inflammatory medicine (NSAID), is subject to pharmacovigilance (PV), which entails tracking its safety profile, spotting possible hazards, and taking precautions to reduce harm. This is a thorough process for ibuprofen pharmacovigilance:

Pre-Marketing Phase

1. Clinical studies: Keep an eye on adverse events (AEs) while conducting clinical trials, paying particular attention to cardiovascular, renal, and gastrointestinal safety.
2. Safety evaluations: Perform comprehensive safety evaluations that include vital sign monitoring and laboratory testing.

Post-Marketing Phase

1. Encourage patients and healthcare providers to report adverse events (AEs) to local or national adverse event reporting systems on their own initiative.
2. PSURs, or periodic safety update reports: Summarize safety data and submit PSURs on a regular basis to regulatory bodies.
3. Signal detection: Keep an eye out for possible safety signals in literature, safety databases, and other sources.
4. Risk management plans (RMPs): Put RMPs into action to reduce hazards that have been recognized, like renal impairment or gastrointestinal bleeding.

Data Collection and Analysis

1. Adverse event reporting forms: To gather AE data, use standardized reporting forms.
2. Database administration: Keep extensive databases for AE data analysis and storage.
3. Statistical analysis: To find trends, patterns, and possible warning signs, use statistical techniques.

Risk Assessment and Mitigation

1. Hazard identification: Determine any possible dangers connected to ibuprofen.
2. Risk characterization: Evaluate the frequency and seriousness of hazards that have been identified.
3. Risk minimization: Put risk-reduction strategies into action, such as changing labels, modifying dosages, or providing focused instruction.

Communication and Collaboration

1. Regulatory agency interactions: Collaborate with regulatory agencies to share safety data and implement risk minimization measures.
2. Healthcare provider education: Provide updates on ibuprofen's safety profile and risk minimization strategies.
3. Patient information: Ensure accurate and up-to-date patient information leaflets.

Continuous Monitoring

1. Continuous literature review: Keep an eye out for fresh safety information in the scientific literature.
2. Signal detection: Keep an eye out for possible safety signals by regularly scanning safety databases and other sources.
3. Regular safety review: Perform thorough safety reviews on a regular basis.

This process guarantees the safe use of ibuprofen in clinical practice by enabling pharmacovigilance efforts to efficiently identify and reduce any possible dangers related to the medication. Ibuprofen , a popular nonsteroidal anti-inflammatory medicine (NSAID), is subject to pharmacovigilance (PV), which entails tracking its safety profile, spotting possible hazards, and taking precautions to reduce harm. This is a thorough process for ibuprofen pharmacovigilance:

Pre-Marketing Phase

1. Clinical studies: Keep an eye on adverse events (AEs) while conducting clinical trials, paying particular attention to cardiovascular, renal, and gastrointestinal safety.
2. Safety evaluations: Perform comprehensive safety evaluations that include vital sign monitoring and laboratory testing.

Post-Marketing Phase

1. Encourage patients and healthcare providers to report adverse events (AEs) to local or national adverse event reporting systems on their own initiative.
2. PSURs, or periodic safety update reports: Summarize safety data and submit PSURs on a regular basis to regulatory bodies.
3. Signal detection: Keep an eye out for possible safety signals in literature, safety databases, and other sources.
4. Risk management plans (RMPs): Put RMPs into action to reduce hazards that have been recognized, like renal impairment or gastrointestinal bleeding.

Data Collection and Analysis

1. Adverse event reporting forms: To gather AE data, use standardized reporting forms.
2. Database administration: Keep extensive databases for AE data analysis and storage.
3. Statistical analysis: To find trends, patterns, and possible warning signs, use statistical techniques.

Risk Assessment and Mitigation

1. Hazard identification: Determine any possible dangers connected to ibuprofen.
2. Risk characterization: Evaluate the frequency and seriousness of hazards that have been identified.
3. Risk minimization: Put risk-reduction strategies into action, such as changing labels, modifying dosages, or providing focused instruction.

Communication and Collaboration

1. Interactions with regulatory agencies: Work together to exchange safety information and put risk reduction strategies into action.
2. Education for healthcare providers: Give them the latest information on the safety profile of ibuprofen and risk-reduction techniques.
3. Patient information: Make sure that patient information pamphlets are correct and current.

Continuous Monitoring

1. Continuous literature review: Keep an eye out for fresh safety information in the scientific literature.
2. Signal detection: Keep an eye out for possible safety signals by regularly scanning safety databases and other sources.
3. Regular safety review: Perform thorough safety reviews on a regular basis.

This process guarantees the safe use of ibuprofen in clinical practice by enabling pharmacovigilance efforts to efficiently identify and reduce any possible dangers related to the medication.

Future perspective with ibuprofen

The first example of an NSAID with demonstrated therapeutic efficacy that is derived from arylpropionic acid is ibuprofen. Its asymmetrical carbon in its chemical structure produces two isomers, R (-) and S (+) ibuprofen, the latter of which is what gives it its pharmacological action. The R (-) isomer undergoes a hepatic bioinversion following the administration of ibuprofen via the racemic pathway, making room for the active S (+) isomer. The development of a specialty

medication that just contains S (+) ibuprofen (Dexibuprofen, Seractil®) in therapeutics opens up new possibilities for this NSAID since it enables the attainment of the same therapeutic benefits as racemic ibuprofen at a lower dosage. Action takes occur within the synovial tissue. In addition to increasing capillar permeability and diffusion through the ibuprofen membrane that is attached to the albumin, the free fraction of ibuprofen is also dispersed throughout the synovial region during inflammatory events.

CONCLUSION

In conclusion, pharmacovigilance for over-the-counter (OTC) drugs such as paracetamol and ibuprofen is essential to ensure their safe and effective use. While these medications are widely used for pain relief and fever reduction, monitoring for adverse effects, particularly in vulnerable populations, is crucial. Paracetamol, when used within recommended doses, is generally safe, but misuse or overdose can lead to severe liver damage. Similarly, ibuprofen, while effective for inflammation and pain, poses risks such as gastrointestinal bleeding or renal issues, especially with long-term use. Ongoing pharmacovigilance efforts, including post-marketing surveillance, are key to identifying potential risks early, updating safety guidelines, and promoting informed use. Healthcare professionals and consumers alike must be educated about proper dosages, contraindications, and the importance of monitoring for side effects to ensure the continued safety of these widely used OTC medications.

REFERENCES

1. WHO Policy Perspectives on Medicines. Geneva: WHO; 2004. Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from: http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf [cited on 2009 Dec 15] [Google Scholar]
2. World Health Organization. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre .Uppsala: Uppsala Monitoring Centre, World Health Organization;2000.
3. Bhangale V. International Marketing Conference on Marketing and Society, IIMK; 2007: 397-402.
4. Sánchez-Sánchez E, Fernández-Cerezo FL, Díaz-Jimenez J, Rosety-Rodriguez M, Díaz AJ, Ordonez FJ, et al. (May 2021). "Consumption of over-the-Counter Drugs: Prevalence and Type of Drugs". International Journal of Environmental Research and Public Health. 18 (11): 5530. doi:10.3390/ijerph18115530. PMC 8196755. PMID 34064096.
5. U.S. Food and Drug Administration: Understanding Over-the-Counter Medicines. https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/default.htm. Accessed 29 Mar 2018.
6. Methodology WCCfDS. Guidelines for ATC classification and DDD assignment 2010. Oslo: World Health Organization; 2009.
7. Prescott LF. Paracetamol: past, present and future. Am J Ther. 2000;7:143–147. [PubMed] [Google Scholar]
8. World Health Organization. How to evaluate the use of medicines by consumers. Geneva: World Health Organization; 2004.
9. Graham GG, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology. 2013;21:201–32.

10. "Ibuprofen". The American Society of Health-System Pharmacists. Archived from the original on 9 September 2017. Retrieved 12 October 2016.
11. "Pedea EPAR". European Medicines Agency (EMA). 29 July 2004. Retrieved 24 February 2024.
12. Halford GM, Lordkipanidze M, Watson SP: 50th anniversary of the discovery of ibuprofen: an interview with Dr Stewart Adams. Platelets. 2012;23(6):415-22. doi: 10.3109/09537104.2011.632032. Epub 2011 Nov 18. [Article]
13. Prescott LF (March 2000). "Paracetamol: past, present, and future". American Journal of Therapeutics. 7 (2): 143–147. doi:10.1097/00045391-200007020-00011. PMID 11319582. S2CID 7754908.
14. Warwick C (November 2008). "Paracetamol and fever management". J R Soc Promot Health. 128 (6): 320–323. doi:10.1177/1466424008092794. PMID 19058473. S2CID 25702228.
15. Saragiotto BT, Abdel Shaheed C, Maher CG (December 2019). "Paracetamol for pain in adults". BMJ. 367: l6693. doi:10.1136/bmj.l6693. PMID 31892511. S2CID 209524643.
16. "Acetaminophen". Physicians' Desk Reference (63rd ed.). Montvale, N.J.: Physicians' Desk Reference. 2009. pp. 1915–1916. ISBN 978-1-56363-703-2. OCLC 276871036.
17. Nam S. "IV, PO, and PR Acetaminophen: A Quick Comparison". Pharmacy Times. Archived from the original on 24 October 2019. Retrieved 24 October 2019.
18. Kis B., Snipes J.A., Busija D.W. Acetaminophen and the cyclooxygenase-3 puzzle: Sorting out facts, fictions, and uncertainties. J. Pharmacol. Exp. Ther. 2005;315:1–7. doi: 10.1124/jpet.105.085431. [PubMed] [CrossRef] [Google Scholar]
19. Aronoff D.M., Oates J.A., Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin. Pharmacol. Ther. 2006;79:9–19. doi: 10.1016/j.clpt.2005.09.009. [PubMed] [CrossRef] [Google Scholar] [Ref list]
20. Bertolini A., Ferrari A., Ottani A., Guerzoni S., Tacchi R., Leone S. Paracetamol: New vistas of an old drug. CNS Drug Rev. Fall-Winter. 2006;12:250–275. doi: 10.1111/j.1527-3458.2006.00250.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]
21. Graham G.G., Scott K.F. Mechanism of action of paracetamol. Am. J. Ther. 2005;12:46–55. doi: 10.1097/00045391-200501000-00008. [PubMed] [CrossRef] [Google Scholar] [Ref list]
22. Roberts L.J., II, Marrow J.D. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman J.G., Limbird L.E., Gilman A.G., editors. Goodman Gilman's the Pharmacological Basis of Therapeutics. 10th ed. McGraw Hill; New York, NY, USA: 2001. pp. 687–731. [Google Scholar] [Ref list]
23. Högestätt E.D., Jönsson B.A., Ermund A., Andersson D.A., Björk H., Alexander J.P., Cravatt B.F., Basbaum A.I., Zygmunt P.M. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J. Biol. Chem. 2005;280:31405–31412. doi: 10.1074/jbc.M501489200. [PubMed] [CrossRef] [Google Scholar] [Ref list]

24. 377:219–229. doi: 10.1007/s00210-008-0284-9. [PubMed] [CrossRef] [Google Scholar] [Ref list] 24]Köfalvi A. Alternative interacting sites and novel receptors for cannabinoid ligands. In: Köfalvi A., editor. Cannabinoids and the Brain. Springer; New York, NY, USA: 2008. pp. 131–160. [Google Scholar] [Ref list]
25. Ottani A., Leone S., Sandrini M., Ferrari A., Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur. J. Pharmacol. 2006;531:280–281. doi: 10.1016/j.ejphar.2005.12.015. [PubMed] [CrossRef] [Google Scholar] [Ref list]
26. Bandschapp O., Filitz J., Urwyler A., Koppert W., Ruppen W. Tropisetron blocks analgesic action of acetaminophen: A human pain model study. Pain. 2011;152:1304–1310. doi: 10.1016/j.pain.2011.02.003. [PubMed] [CrossRef] [Google Scholar] [Ref list]
27. Pickering G., Faure M., Commun F., de Boissy E.C., Roche G., Mom T., Simen E., Dubray C., Eschalier A., Gilain L. Tropisetron and paracetamol association in post-operative patients. Fundam. Clin. Pharmacol. 2012;26:432–437. doi: 10.1111/j.1472-8206.2011.00933.x. [PubMed] [CrossRef] [Google Scholar] [Ref list]
28. Pini L.A., Vitale G., Ottani A., Sandrini M. Naloxone-reversible antinociception by paracetamol in the rat. J. Pharmacol. Exp. Ther. 1997;280:934–940. [PubMed] [Google Scholar] [Ref list]
29. Ruggieri V., Vitale G., Pini L.A., Sandrini M. Differential involvement of opioidergic and serotonergic systems in the antinociceptive activity of N-arachidonoyl-phenolamine (AM404) in the rat: Comparison with paracetamol. Naunyn Schmiedebergs Arch. Pharmacol. 2008; 377:219–229. doi: 10.1007/s00210-008-0284-9. [PubMed] [CrossRef] [Google Scholar] [Ref list]
30. Pickering G., Kastler A., Macian N., Pereira B., Valabrègue R., Lehericy S., Boyer L., Dubray C., Jean B. The brain signature of paracetamol in healthy volunteers: A double-blind randomized trial. Drug Des. Dev. Ther. 2015;9:3853–3862. doi: 10.2147/DDDT.S81004. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]
31. Pickering G., Macian N., Dubray C., Pereira B. Paracetamol sharpens reflection and spatial memory: A double-blind randomized controlled study in healthy volunteers. Drug Des. Dev. Ther. 2016;10:3969–3976. doi: 10.2147/DDDT.S111590. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]
32. Borne R.F. Nonsteroidal Anti-inflammatory Drugs. In: Foye W.O., Lempke T.L., Williams D.A., editors. Principles of Medicinal Chemistry. 4th ed. Williams and Wilkins; Baltimore, MD, USA: 1995. pp. 544–545. [Google Scholar] [Ref list]
33. Dong H., Haining R.L., Thummel K.E., Rettie A.E., Nelson S.D. Involvement of human cytochrome P450 2D6 in the bioactivation of acetaminophen. Drug Metab. Dispos. 2000;28:1397–1400. [PubMed] [Google Scholar] [Ref list]
34. Prescott LF (October 1980). "Kinetics and metabolism of paracetamol and phenacetin". British Journal of Clinical Pharmacology. 10 (Suppl 2): 291S–298S. doi:10.1111/j.1365-2125.1980.tb01812.x. PMC 1430174. PMID 7002186.
35. Forrest JA, Clements JA, Prescott LF (1982). "Clinical pharmacokinetics of paracetamol". Clin Pharmacokinet. 7 (2): 93–107. doi:10.2165/00003088-198207020-00001. PMID 7039926. S2CID 20946160.

36. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF (June 2013). "The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity, and recent pharmacological findings". Inflammopharmacology. 21 (3): 201–232. doi:10.1007/s10787-013-0172-x. PMID 23719833. S2CID 11359488.
37. Marx J, Walls R, Hockberger R (2013). Rosen's Emergency Medicine – Concepts and Clinical Practice. Elsevier Health Sciences. ISBN 9781455749874.
38. Nimmo J, Heading RC, Tothill P, Prescott LF (March 1973). "Pharmacological modification of gastric emptying: effects of propantheline and metoclopromide on paracetamol absorption". Br Med J. 1 (5853): 587–9. doi:10.1136/bmj.1.5853.587. PMC 1589913. PMID 4694406.
39. Toes MJ, Jones AL, Prescott L (2005). "Drug interactions with paracetamol". Am J Ther. 12 (1): 56–66. doi:10.1097/00045391-200501000-00009. PMID 15662293. S2CID 39595470.
40. Conaghan PG, Arden N, Avouac B, Migliore A, Rizzoli R (April 2019). "Safety of Paracetamol in Osteoarthritis: What Does the Literature Say?". Drugs Aging. 36 (Suppl 1): 7–14. doi:10.1007/s40266-019-00658-9. PMC 6509082. PMID 31073920.
41. Keaveney A, Peters E, Way B (September 2020). "Effects of acetaminophen on risk taking". Social Cognitive and Affective Neuroscience. 15 (7): 725–732. doi:10.1093/scan/nsaa108. PMC 7511878. PMID 32888031.
42. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. (March 2016). "Paracetamol: not as safe as we thought? A systematic literature review of observational studies". Ann Rheum Dis. 75 (3): 552–9. doi:10.1136/annrheumdis-2014-206914. PMC 4789700. PMID 25732175.
43. Choueiri TK, Je Y, Cho E (January 2014). "Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies". Int J Cancer. 134 (2): 384–96. doi:10.1002/ijc.28093. PMC 3815746. PMID 23400756.
44. McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ (October 2018). "Long-term adverse effects of paracetamol – a review". Br J Clin Pharmacol. 84 (10): 2218–2230. doi:10.1111/bcp.13656. PMC 6138494. PMID 29863746.
45. Eyers S, Weatherall M, Jefferies S, Beasley R (April 2011). "Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis". Clinical and Experimental Allergy. 41 (4): 482–9. doi:10.1111/j.1365-2222.2010.03691.x. PMID 21338428. S2CID 205275267.
46. Fan G, Wang B, Liu C, Li D (2017). "Prenatal paracetamol use and asthma in childhood: A systematic review and meta-analysis". Allergol Immunopathol (Madr). 45 (6): 528–533. doi:10.1016/j.aller.2016.10.014. PMID 28237129.
47. Stevens–Johnson syndrome. In: Wikipedia [Internet]. 2020 [cited 2020]. Available from: https://en.wikipedia.org/w/index.php?title=Stevens%E2%80%93Johnson_syndrome&oldid=937266764
48. Nigerian Journal of Clinical Practice - Drug-induced Stevens–Johnson syndrome in Indian population: A multicentric retrospective analysis : Download PDF [Internet]. [cited 2020]. Available from: http://www.njcponline.com/downloadpdf.asp?issn=1119 3077;year=2017;volume=20;issue=8;spage=978;epage=983;aulast=Hirapara;type=2

49. Stevens-Johnson syndrome - Symptoms and causes - Mayo Clinic [Internet]. [cited 2020]. Available from: https://www.mayoclinic.org/diseases-conditions/stevens-johnson-syndrome/symptoms-causes/syc-20355936
50. Warwick C (November 2008). "Paracetamol and fever management". J R Soc Promot Health. 128 (6): 320–323. doi:10.1177/1466424008092794. PMID 19058473. S2CID 25702228.
51. Li S, Yue J, Dong BR, Yang M, Lin X, Wu T (July 2013). "Acetaminophen (paracetamol) for the common cold in adults". Cochrane Database Syst Rev. 2013 (7): CD008800. doi:10.1002/14651858.CD008800.pub2. PMC 7389565. PMID 23818046.
52. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S (2006). "Paracetamol: new vistas of an old drug". CNS Drug Rev. 12 (3–4): 250–75. doi:10.1111/j.1527-3458.2006.00250.x. PMC 6506194. PMID 17227290.
53. Saragiotto BT, Abdel Shaheed C, Maher CG (December 2019). "Paracetamol for pain in adults". BMJ. 367: l6693. doi:10.1136/bmj.l6693. PMID 31892511. S2CID 209524643.
54. MJ, Silberstein SD, Schwedt TJ (January 2015). "The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies". Headache. 55 (1): 3–20. doi:10.1111/head.12499. PMID 25600718. S2CID 25576700.
55. Derry S, Moore RA (2013). "Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults". Cochrane Database Syst Rev. 4 (4): CD008040. doi:10.1002/14651858.CD008040.pub3. PMC 4161111. PMID 23633349.
56. Mayans L, Walling A (February 2018). "Acute Migraine Headache: Treatment Strategies". Am Fam Physician. 97 (4): 243–251. PMID 29671521.
57. Kindy D. "The Inventor of Ibuprofen Tested the Drug on His Own Hangover". Smithsonian Magazine. Retrieved 3 July 2021. Stewart Adams and his associate John Nicholson invented a pharmaceutical drug known as 2-(4-isobutylphenyl) propionic acid.
58. Halford GM, Lordkipanidzé M, Watson SP (2012). "50th anniversary of the discovery of ibuprofen: an interview with Dr Stewart Adams". Platelets. 23 (6): 415–422. doi:10.3109/09537104.2011.632032. PMID 22098129. S2CID 26344532.
59. Adams SS, McCullough KF, Nicholson JS: The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. Arch Int Pharmacodyn Ther. 1969 Mar;178(1):115-29. [Article]
60. Rao P, Knaus EE (September 2008). "Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond". Journal of Pharmacy & Pharmaceutical Sciences. 11 (2): 81s–110s. doi:10.18433/J3T886. PMID 19203472.
61. Kakuta H, Zheng X, Oda H, Harada S, Sugimoto Y, Sasaki K, et al. (April 2008). "Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor". Journal of Medicinal Chemistry. 51 (8): 2400–2411. doi:10.1021/jm701191z. PMID 18363350.
62. Mazaleuskaya LL, Theken KN, Gong L, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics. 2015

Feb;25(2):96-106. [PMC free article] [PubMed] [Reference list]

63. Bagher AM. Association of CYP2C9∗3 and CYP2C8∗3 Non-Functional Alleles with Ibuprofen-Induced Upper Gastrointestinal Toxicity in a Saudi Patient. Case Rep Med. 2023;2023:6623269. [PMC free article] [PubMed] [Reference list]
64. Su J, Zhang C, Su Y, Huang C, Zhao J, Yang H, Xu Z, Li J, Yang X. Pharmacokinetics, Bioequivalence, and Safety Evaluation of Two Formulations of 0.2-g Ibuprofen Granules. Clin Pharmacol Drug Dev. 2023 Jun;12(6):588-593. [PubMed]
65. Weng SE, Hsu WT, Hsiao FY, Lee CM. Non-steroidal anti-inflammatory drugs, renin-angiotensin system blockade or diuretics and risk of acute kidney injury: A case-crossover study. Arch Gerontol Geriatr. 2024 Aug;123:105394. [PubMed] [Reference list]
66. Hassan S, Khalid F, Alirhayim Z, Amer S. Lithium toxicity in the setting of nonsteroidal anti-inflammatory medications. Case Rep Nephrol. 2013;2013:839796. [PMC free article] [PubMed] [Reference list]
67. Gomez Lumbreras A, Reese TJ, Del Fiol G, Tan MS, Butler JM, Hurwitz JT, Brown M, Kawamoto K, Thiess H, Wright M, Malone DC. Shared Decision-Making for Drug-Drug Interactions: Formative Evaluation of an Anticoagulant Drug Interaction. JMIR Form Res. 2022 Oct 19;6(10):e40018. [PMC free article] [PubMed] [Reference list]
68. "Ibuprofen". The American Society of Health-System Pharmacists. Archived from the original on 9 September 2017. Retrieved 12 October 2016.
69. Rossi S, ed. (2013). Australian Medicines Handbook (2013 ed.). Adelaide: The Australian Medicines Handbook Unit Trust. ISBN 978-0-9805790-9-3.
70. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. (December 2012). "Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project)". Drug Safety. 35 (12): 1127–46. doi:10.1007/BF03261999. PMC 3714137. PMID 23137151.
71. Ayres JG, Fleming DM, Whittington RM (May 1987). "Asthma death due to ibuprofen". Lancet. 1 (8541): 1082. doi:10.1016/S0140-6736(87)90499-5. PMID 2883408. S2CID 38589434.
72. Christa Aungst, Alussa Billingsles, “Effect of Ibuprofen on Liver & Kidney”2022;3(1):4-8
73. Mărginean MO, Meliț LE, Mocanu S, Săsăran V. Ibuprofen, a Potential Cause of Acute Hemorrhagic Gastritis in Children - A Case Report. J Crit Care Med (Targu Mures). 2018 Oct;4(4):143-146. [PMC free article] [PubMed]
74. Thibaut C, Hazard A, Huon C, Desfrere L. Effect of ibuprofen on bilirubin-albumin binding during the treatment of patent ductus arteriosus in preterm infant. J Matern Fetal Neonatal Med. 2011 Nov;24 Suppl 3:7-9. [PubMed] [Reference list]
75. Watanabe T, Abe M, Tada F, Aritomo K, Ochi H, Koizumi Y, Tokumoto Y, Hirooka M, Kumagi T, Ikeda Y, Matsuura B, Hiasa Y. Drug-induced liver injury with serious multiform exudative erythema following the use of an over-the-counter medication containing ibuprofen. Intern Med. 2015;54(4):395-9. [PubMed] [Reference list]
76. Marin Anthony Christopher Manoukian, Christopher William Migdal Amode RavindraTembhekar Jerad Alexander Harris and Charles DeMesa, “Topical Administration of Ibuprofen for Injured Athletes: Considerations, Formulations, and

Comparison to Oral Delivery" Manoukian et al. Sports Medicine Open 2017;7(2):1-9

77. "10.1.1 Non-steroidal anti-inflammatory drugs". British National Formulary. Archived from the original on 17 November 2016. Retrieved 13 April 2016.
78. Joint Formulary Committee (2013). British National Formulary (BNF) (65 ed.). London, UK: Pharmaceutical Press. pp. 665, 671. ISBN 978-0-85711-084-8.
79. Alabed S, Cabello JB, Irving GJ, Qintar M, Burls A (August 2014). "Colchicine for pericarditis" (PDF). The Cochrane Database of Systematic Reviews (Review). 2014 (8): CD010652. doi:10.1002/14651858.CD010652.pub2. PMC 10645160. PMID 25164988.
80. Rostas SE, McPherson CC (2016). "Pharmacotherapy for Patent Ductus Arteriosus: Current Options and Outstanding Questions". Current Pediatric Reviews (Review). 12 (2): 110–119. doi:10.2174/1573396312021605060028. PMID 27197952.
81. Bhushan R, Martens J. Dissolution of enantiomers of ibuprofen by liquid chromatography: a review. Biomed. Chromatogr 1998; 12(6):309-316.
82. Jones K, Seymour RA, Hawkesford JE. Synergistic interactions between the dual serotonergic, noradrenergic reuptake inhibitor duloxetine and the non-steroidal anti-inflammatory drug ibuprofen in inflammatory pain in rodents. British Journal of Oral and Maxilofacial surgey 1997; 35(3):173-176.
83. Wagner W, Khanna P, Furst DE. Non-steroidal-anti inflammatory drugs, disease modifying anti rheumatic drugs, non opioid analgesics and drugs used in Gout. In: Katzung BG editor. Basic and clinical pharmacology 9th ed., McGraw hill Booston, 2004. p. 585.
84. Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. J Clin Pharmacol 2003 Sep;43(9):968-973.
85. Kravs DM, Pharm JT. Neonatal therapy. In: Koda-Kimble MA, Young LV, Kradjan WA, Guglielmo BJ, Alldredge BK and Corelli RL editors. Applied therapeutics: the clinical use of drugs, 8th ed., Lipponcott William and Wilkins A Wolters Kluwer company Philadelphia New York, 2005. p. 94-23.
86. Konstan MW, Krenicky JE, Finney MR, Kirchner HL, Hilliard KA, Hilliard JB, et al. Effect of ibuprofen on neutrophil migration in vivo in cystic fibrosis and healthy subjects. J Pharmacol Exp Ther 2003 Sep;306(3):1086-1091.
87. Mackey JE, Anbar RD. High-dose ibuprofen therapy associated with esophageal ulceration after pneumonectomy in a patient with cystic fibrosis: a case report. BMC Pediatr 2004 Sep;4:19.
88. Rifai N, Sakamoto M, Law T, Galpchian V, Harris N, Colin AA. Use of a rapid HPLC assay for determination of pharmacokinetic parameters of ibuprofen in patients with cystic fibrosis. Clin Chem 1996 Nov;42(11):1812-1816.
89. Dickinson BD, Altman RD, Deitchman SD, Champion HC. Safety of over-the counter inhalers for asthma: Report of the council on scientific affairs. Chest. 2000;118(2):522-6. doi: 10.1378/chest.118.2.522, PMID 10936150.
90. Ferner RE, Beard K. Over the counter medicines: Proceed with caution. BMJ. 2008;336(7646):694-6. doi: 10.1136/bmj.39504.389676.AD, PMID 18369225.
91. Foley M, Breindahl T, Hindersson P, Deluca P, Kimergård A. Misuse of 'over the-counter' codeine analgesics: Does formulation play a

role? Public Health. 2016;130:95-6. doi: 10.1016/j.puhe.2015.10.006, PMID 26612458.

92. Barrenberg E, Garbe E. Use of over-the-counter (OTC) drugs and perceptions of OTC drug safety among German adults. Eur J Clin Pharmacol. 2015;71(11):1389-96. doi: 10.1007/s00228-015-1929-5, PMID 26300207.
93. Bennadi D. Self-medication: A current challenge. J Basic Clin Pharm. 2013;5(1):19-23. doi: 10.4103/0976-0105.128253, PMID 24808684.
94. Lynch SS. Overview of over-the-counter drugs. MSD Manual [internet]; 2019. Health Care. Available from: https://www.msdmanuals.com/en-in/home/drugs/ over-the-counter-drugs/overview-of-over-the-counter-drugs [cited 21/3/2022].
95. Marathe PA, Kamat SK, Tripathi RK, Raut SB, Khatri NP. Over-the-counter medicines: Global perspective and Indian scenario. J Postgrad Med. 2020;66(1):28-34. doi: 10.4103/jpgm.JPGM_381_19, PMID 31898596.
96. Dickinson BD, Altman RD, Deitchman SD, Champion HC. Safety of over-the counter inhalers for asthma: Report of the council on scientific affairs. Chest. 2000;118(2):522-6. doi: 10.1378/chest.118.2.522, PMID 10936150.
97. Paracetamol 500 mg tablets – summary of product characteristics (SmPC) - (eMC) [online]. http://medicines.org.uk. Available at https://www.medicines.org.uk/emc/product/4195 (last accessed 8 January 2018).
98. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. Pediatric Anesthesia [Internet]. 2008 [07.05.2024].
99. Upfal J. Australian drug guide : the plain language guide to drugs and medicines of all kinds. Melbourne, Vic.: Black Inc.; 2016 [05.06.2024]. Available from: https://adf.on.worldcat.org/oclc/935401237.
100. Narayan K, Cooper S, Morphet J, Innes K. Effectiveness of paracetamol versus ibuprofen administration in febrile children: A systematic literature review. J Paediatr Child Health. 2017 Aug;53(8):800-807. [PubMed] [Reference list]
101. Luo S, Ran M, Luo Q, Shu M, Guo Q, Zhu Y, Xie X, Zhang C, Wan C. Alternating Acetaminophen and Ibuprofen versus Monotherapies in Improvements of Distress and Reducing Refractory Fever in Febrile Children: A Randomized Controlled Trial. Paediatr Drugs. 2017 Oct;19(5):479-486. [PubMed] [Reference list]

HOW TO CITE: Vrushali Gaikwad*, Sonal Kumbhar, Dr. Nilesh Chougule, Pharmacovigilance and Over Counter Drugs Ensuring Safety, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 12, 1193-1212. https://doi.org/10.5281/zenodo.14361696